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EXAMINER	
KELLY, ROBERT M	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/971,773	KANDA ET AL.	
	Examiner	Art Unit	
	Robert M Kelly	1632	

-- The MAILING DATE of this communication appears on the cov r sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-64* is/are pending in the application.

4a) Of the above claim(s) *2,3,20-22,24-30 and 41-61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,12-19,23, 31-40, and 62-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 4, 12-19, 23 and 31-40 are considered.

Election/Restrictions

Applicant's election of Group II, Claims 1, 4-19, and 23-40 in Applicant's Amendment, dated December 8, 2003, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicant's further elected the following species with regard to Group II: (1) a CHO cell; (2) a gene disruption technique targeting a gene encoding the enzyme as the method to produce the cell; and (3) the enzyme α-1,6-fucosyltransferase as the enzyme that is disrupted, in lieu of the election of one of the GDP-fucose enzymes of claim 5.

For the reasons given above, Claims 5-11 and 24-30 have been withdrawn from consideration, as drawn to a non-elected species, and Claims 1, 4, 12-19, 23, 31-40 and newly presented Claims 62-64 will be considered only with respect to those elected species above. The withdrawn claims, Claims 5-11 and 24-30 will be rejoined for consideration, along with the other non-elected species upon allowance of all of the elected subject matter.

Priority

If applicant desires priority under 35 U.S.C. 119(e) based upon a previously filed application, specific reference to the earlier filed application must be made in the instant application. For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the

relationship (i.e., continuation, divisional, or continuation-in-part) of the applications. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph unless it appears in an application data sheet. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No. _____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

If the application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A priority claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed claim for priority under 35 U.S.C. 119(e), 120, 121 and 365(c). The

petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

It is noted that Applicants have claimed foreign priority benefits under 35 USC 119/365 to Japanese Application No. P. 2000-308526, filed October 6, 2000, and under 35 USC 120/365 to PCT/JP01/08804, filed October 5, 2001.

Moreover, while the PCT document may be obtained, a certified copy of the Japanese Application, translated into English, is required.

Specification

The disclosure is objected to because of the following informalities:

(1) page 4, line 29 cites "Biochemistry, 36, 130 (1997)" however, no such citation exists, and, moreover, the sentence for which this citation is given is unclear – what variety exists?

Appropriate correction is required.

Claim Objections

Claim 1 is objected to because of the following informalities: a CHO cell is inherently derived from Chinese hamster ovary tissue. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4 and 12-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

With regard to Claim 4, it is unclear how much the activity of an enzyme relating to the modification of a sugar chain in which fucose is bound to the 6-position of N-acetylglucosamine in the reducing end through α(1→6)glycosyl bond in the complex N-glycoside-linked sugar chain must be decreased.

With regard to Claims 13-19, the claims are rejected as depending on a rejected base claim.

Claims 23 and 31-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

With regard to Claim 23, it is unclear how much an activity relating to the modification of a sugar chain wherein fucose is bound to the 6-position of N-acetylglucosamine in the reducing end through α(1→6)glycosyl bond in the complex N-glycoside-linked sugar chain must be decreased.

With regard to Claims 31-40, the claims are rejected as depending on a rejected base claim.

Claim 19 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 19 recites the limitation "wherein the sugar chain to which fucose is not bound is a complex N-glycoside-linked sugar chain in which fucose is not bound to the 6-position of N-acetylglucosamine in the reducing end through α(1→6)glycosyl bond." It is not clear how a sugar chain in which fucose is not bound, could be bound through a specific bond.

Claims 62-63 are rejected under 35 U.S.C. 112, second paragraph, as failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 62 does not further limit the claims from which it depends, because Claim 1, from it depends, through Claim 4, contains all the limitations of Claim 62.

Claim 63 requires the fucose which are not bound in Claim 1 to not be bound through a specific linkage. It is unclear how, if such residues are not bound at all, they could have been otherwise bound through a specific linkage.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4, 12-19, 23, 31-40 and 62-64 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a CHO cell comprising a deletion of at least exon 2 of one FUT8 gene, which deletion produces a non-functional enzyme, into which a gene encoding an antibody is introduced, such antibody gene being expressed and producing antibodies having complex N-glycoside-linked sugar chains bound to the Fc region, wherein among the total complex N-glycoside-linked sugar chains bound to the Fc region in the composition, the ratio of a sugar chain in which fucose is not bound to N-acetylglucosamine at the 6 position is 20% or more, does not reasonably provide enablement for any CHO cell or any CHO cell comprising any deletion of a gene encoding FUT8 that produces any decrease in such enzyme, into which a gene encoding an antibody is introduced, such antibody gene being expressed and producing antibodies having complex N-glycoside-linked sugar chains bound to the Fc region, wherein among the total complex N-glycoside-linked sugar chains bound to the Fc region in the composition, the ratio of a sugar chain in which fucose is not bound to N-acetylglucosamine is 20% or more. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Background

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by Applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ.2d at 1404. Such factors are:

(1) The breadth of the claims;

(2) The nature of the invention;

(3) The state of the art;

(4) The level of one of ordinary skill in the art;

(5) The level of predictability in the art;

(6) The amount of direction and guidance provided by Applicant;

(7) The existence of working examples; and

(8) The quantity of experimentation needed to make and/or use the invention.

These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention within its fully-claimed scope, and that, therefore, Applicant's claims are not enabled to their fully-claimed scope.

The Breadth of the Claims

Claims 1, 4, 12-19, 23, and 31-40 are broad in scope. The following paragraphs will outline the full scope of each of these claims. (Applicant is reminded that the invention is only being analyzed to the scope of the species elections made by Applicant, i.e., (1) a CHO cell; (2) a gene disruption technique targeting a gene encoding the enzyme as the method to produce the cell; and (3) the enzyme α-1,6-fucosyltransferase as the enzyme that is disrupted, and that therefore, the outlined scope of the Claims below does not necessarily reflect the actual scope of the claims.)

Claims 1, 4, 12-19, and 62-64 encompass any CHO cell into which any antibody-encoding gene is introduced and in which the antibody is expressed, thereby making antibodies with N-glycoside linked sugar chains in which 80% or less of these sugar chains contain fucose bound to N-acetyl glucoseamine in the reducing end of the sugar chains. Claim 4 limits the CHO cell to one in which the activity of α-1,6-fucosyltransferase is decreased by any amount or deleted. Claim 12 limits the decreased or deleted enzyme to α-1,6-fucosyltransferase. Claim 13 limits the α-1,6-fucosyltransferase to SEQ ID NO 1 or any sequence hybridizing to SEQ ID NO 1 under stringent conditions. Claim 14 limits the α-1,6-fucosyltransferase that is decreased or deleted in Claim 12 to those described by SEQ ID NO 23 or those of SEQ ID NO 23 having any at least one insertion, deletion, substitution, or added amino acid, which also has α-1,6-fucosyltransferase activity, or any amino acid sequence with at least 80% homology with SEQ ID NO 23 and having α-1,6-fucosyltransferase activity. Claim 15 limits the CHO cell of Claim 4 to those in which any gene disruption technique targeting the encoded enzyme has been used to produce the deleted or decreased α-1,6-fucosyltransferase activity. Claim 16 encompasses any CHO cells of Claim 4 that is additionally resistant to any lectin that binds the fucose α(1→6) N-acetylglucosamine on the reducing end of any sugar chain. Claim 17 limits Claim 4 to CHO cells that produce antibody compositions have any amount higher antibody-dependent cytotoxic acitivity than its parent CHO. Claim 18 limits the CHO cell of Claim 17 to those cells that produce antibodies with a higher antibody-dependent cytotoxicity activity higher than antibody compositions in which more than 80% of the sugar chains have fucose α(1→6) N-acetylglucosamine on the reducing end. Claim 19 limits Claim 18 to those that produce sugar chains in which fucose is not bound, to those not bound by an α(1→6) linkage at the reducing

end, to N-acetylglucoseamine. Claim 62 limits the cells of Claim 4 to the same ratios of fucose as Claim 1. Claim 63 requires the linkage through which the fucose is not bound in Claim 4, to be an α(1→6) linkage. Claim 64 requires the antibody molecule of Claim 4 to be an IgG molecule.

Claims 23 and 31-40 are drawn to any CHO cell in which the activity of α-1,6-fucosyltransferase is decreased or deleted by a gene disruption technique. Claim 31 limits the enzyme to α-1,6-fucosyltransferase. Claim 32 limits Claim 31 to the DNA sequences comprising either SEQ ID NO 1, or any sequences hybridizing to SEQ ID NO 1 under stringent conditions, or sequences comprising SEQ ID NO 2, or any sequence hybridizing to SEQ ID NO 2 under stringent conditions. Claim 33 limits the protein encoded in Claim 31 to those comprising SEQ ID NO 23 or SEQ ID NO 24, or those sequences having any one or more deletions/insertions/substitutions or additions to either SEQ ID NOS 23 or 24, or any sequence that is 80% or more homolgous to SEQ ID NOS 23 or 24. Claim 34 limits the CHO cell of Claim 23 to one produced by any gene disruption technique. Claim 35 limits Claim 23 to CHOs which are resistant to lectins that recognize fucose bound to N-acetylglucosamine though an α(1→6) linkage at the reducing end. Claim 36 limits the cell of Claim 23 to any CHO cell. Claim 37 limits Claim 23 to any CHO into which a gene encoding any antibody is introduced. Claim 38 limits the antibody to any IgG class antibodies. Claim 39 encompasses a method of producing of an antibody composition with the cells of Claim 37, by culturing the cells and recovering the antibody composition from the culture. Claim 40 limits the method Claim 39 to producing antibodies having a higher antibody-dependent cell-mediated cytotoxic activity than the parent cell would produce.

Because these claims encompass a wide variety of CHO cells, a wide variety of mutations to α-1,6-fucosyltransferase, and a wide variety of antibody molecules, having a wide range of fucose compositions, the detail of the disclosure provided by Applicant, in view of the prior art, must encompass a wide area of knowledge to a reasonably comprehensive extent. In other words, those aspects considered broad must be fleshed out to a reasonable extent so that one of ordinary skill in the art, at the time of invention by Applicant (hereinafter the "Artisan"), would be able to practice the invention, and do so to the fully-claimed scope of the invention, without an undue burden being impose such Artisan (undue burden). However, as will be discussed below, this burden has not been met.

The Nature of the Invention

The invention is in the nature of transgenic CHO cells comprising modifications to the glycosylation enzymes to produce transgenic antibodies with higher antibody-dependent cytotoxicity. Such support for this may be found in the specification (pp. 1-9). It is noted that some of Applicant's claims do not even require the production of antibodies, and the Examiner does not see any use for such CHO cells other than to produce antibodies with higher antibody-dependent cytotoxicity (Claims 23, 31-36).

The production of antibodies having different glycosylation characteristics from cells of different species and strains is known in the art, but highly unpredictable. Such is borne out in Raju, et al. (2000) Glycobiology, 10(5): 477-86, p. 483, which indicates (1) speicies variability in glycosylation in IgG antibodies, and (2) within a species, variability in the amounts of specific sugars. Therefore, the art of glycosylation is highly unpredictable, and new inventions in the

field would require a showing that the cell produces the correct types of glycosylation for the antibodies produced from it, as well as in the correct amounts.

With regard to the production of mutations in α-1,6-fucosyltransferase that decrease or completely remove the activity of such enzyme, the nature of this is unpredictable. The Artisan would not be able to reasonably predict that any specific insertion/deletion/substitution or addition or any sequence with 80% homology or sequence identity or hybridizing to the claimed sequences would produce an enzyme with sufficiently reduced activity to produce the claimed glycosolations in any antibody transgenically made in such cells. Such wide variety of changes would need to be determined for the function of the enzyme on a case-by-case basis. Stryer (1988) Biochemistry, 3rd Ed., Freeman and Co., New York, NY, pp. 35-37 underscores the unpredictability of such changes, emphasizing that secondary structure, at the core of protein folding and therefore activity, stating that "*The context in which a peptide segment folds may be crucial.*" (p. 37). What Stryer is getting at here, is that any change in the protein sequence may cause changes to secondary structure, which would then be amplified to higher levels of structure, causing the protein so modified to fold improperly, and altering its function, but such is still unpredictable, even at the level of secondary structure, have only about 60% predictability with the then-known structures. Moreover, Stryer states, "These are encouraging starts, but it is evident that much remains to be accomplished." The influence of such small changes on overall structure, and therefore function, cannot be underestimated, and therefore, it is not predictable that the widely varied changes encompassed by Applicant's claimed invention are not reasonably predictable by the Artisan.

In view of the nature of the invention, the Artisan would require a reasonable assurance that the cells and mutations would produce such altered glycosylation patterns, and produce these antibodies with higher antibody dependent cytotoxicity. Alternatively, direct examples of such would overcome such burden, as if the invention worked for a specific mutation, then it had to have met the requirements.

The State of the Prior Art

The state of the prior art is similarly unenabling for new inventions in the field. With respect to transgenic CHO cells comprising modifications to the glycosylation enzymes to produce transgenic antibodies with higher antibody-dependent cytotoxicity, the unpredictable nature is borne out by the recent article by Shinkawa, et al. (2003) J. Biol. Chem., 278(5): 3466-3473. In Shinkawa, conflicting reports are reviewed for various sugars present in the glycosylated enzyme (e.g., pp. 3471-72, paragraph bridging pages). Moreover, Shinkawa demonstrates the absence of predictability in the field by finding results that conflict with the then-current data, i.e., p. 3472, paragraph bridging columns, and an admission that they were "speculating" when they decided to investigate the contribution of fucose residues to ADCC activity (p. 3472, col. 2, first full paragraph).

With regard the prior art of protein structure and function prediction, and specifically, where and how many mutations may be made within an expressed protein to produce lowered, yet present activities of the protein, the art is similarly unenabling. A recent review by Jones (2001) Pharmacogenomics J., 1(2): 126-34, underscores the fact that the art is not enabling of any mutations, as it is unpredictable. In Jones, the author reviews a series of computational methods used for protein structure, and therefore function, prediction (ABSTRACT), and finds

that "Despite the evident improvements in automatic alignment accuracy in CASP4 [, a general symposium of experts in protein structure fields, providing a survey of methods that would be used to make predictions of the influence of changes to known proteins], there is still a lot to criticize in the comparative modeling field, at least as viewed in the CASP experiment ...." (p. 127, col. 2). Indeed, Jones concludes that "there is still a lot of work to do." And that there exists many problems with each method of structure prediction (CONCLUSIONS in general).

Hence, because the nature of the invention and state of the art evinces a level of unpredictability in the art, as discussed above, and because the art for glycosylation influcences on antibody-dependent cytotoxicity provides not only unpredictable, but conflicting results, absent a largely enabling disclosure by Applicant, by way of specific direction and guidance and examples, the invention claimed by Applicant is not enabled for its fully-claimed scope.

The Level of One of Ordinary Skill in the Art at the Time of Invention

The level of one of skill in the art at the time of invention was advanced, being that of a person holding a Ph.D. or an M.D.; however, because of the immaturity of the art, and its unpredictability, as shown by the other factors, one of skill in the art at the time of invention by Applicant would not have been able to make and/or use the invention claimed, to its fully-claimed scope, without undue experimentation.

The Level of Predictability in the Art

Because the art as shown above discloses conflicting evidence for the roles of sugar residues in antibody-dependent cytotoxicity, and the art does not show an ability to reasonably predict the structure, and therefore function, of an enzyme, after mutating the enzyme in any way, the Artisan would not be able to reasonably predict, in the absence of proof to the contrary,

that such a wide variety of mutations the fucosyltransferase would produce less active enzyme, or that any specific glycosylation would produce higher levels of antibody dependent cytotoxicity.

Hence, absent a strong showing of guidance and direction and/or working examples demonstrating the same, such invention as claimed by Applicant, is not enabled for its fully-claimed scope, because the Artisan could not reasonably predict that such methods would be able to be made, or produce useful product if they were made.

The Amount of Direction and Guidance Provided by Applicant

The specification broadly discusses the pathways involved in glycosylation of proteins in general and the structure of glycosylations, pointing out that it is involves many enzymes that remove and add and modify the glycosylation chains and that the complexity makes it difficult to control such activities, so that a solution to the pathways and their regulation needs to be reached through trial and error (pp. 1-9, p. 9). A summary tracking the claims is then given (pp. 9-24), followed by a brief explanation of the drawings (pp. 24-33). The detailed description discusses, in broad terms, cells and antibodies with glycosylations that represent the claimed invention (pp. 34-46), followed by a broad discussion of the fucosyltransferase enzyme, broadly claiming sequences that hybridize to disclosed sequences under example "stringent" conditions, an broadly discussing such conditions, however such sequences are required to have the activity of the fucosyltransferase enzyme (p. 46). Also, protein sequences of the enzyme are broadly discussed, but require such function of the enzyme itself again (p. 46). Pages 47-48 continue to broadly discuss such requirements, and 48-51 discuss general methods of making such mutant cells and enzymes. Pages 51-115 broadly discuss preparation of host cells, enzyme mutations,

lectin resistant cells, transgenic humans, animals and plants, methods of preparing antibody compositions from the cells, construction of chimeric antibodies, humanized antibodies, glycosylation analysis, and applications of the antibodies of the invention.

However, outside of these broad teachings and assertions, little direction and guidance is given as to how to predict that any specific mutation would produce functional, albeit less functional than wild-type activity in fucosyltransferse, and that such antibodies with the required fucose absent in more than 20% of the glycosylations would produce higher levels of antibody-dependent cytotoxicity.

Because of the lack of direction and guidance that would allow the Artisan to reasonably predict that such mutations would produce the required activity of the fucosyltransferse, and the activity would be reduced to such an extent as required to produce such glycosylations, and that such glycosylated antibody would be produced, and that such glycosylated antibody would then exhibit higher than normal antibody-dependent cytotoxicity, the examples would be required to provide a very strong showing of effectiveness. Absent this strong showing in the examples, it would have required undue experimentation to make and/or use the invention within the fully-claimed scope, as claimed by Applicant.

The Existence of Working Examples

Example 1 demonstrates the production of anti-ganglioside GD3 human chimeric antibodies in a few cell lines, including CHO cells. Example 2 demonstrates the activity evaluation of such antibodies produced, demonstrating a correlation with the fucose present in the glycosylation. Example 3 demonstrates another antibody preparation in various cell lines. Example 4 demonstrates evaluates the activity of these other antibodies preparations, and finds

that the antibody dependent cytotoxicity varies with cell line, and implicates the fucose present in the glycosylation again. Example 4 analyzes the sugar content, underscoring the fucose correlation to antibody dependent cytotoxicity. Example 6 demonstrates the separation of those antibodies having higher antibody dependent cytotoxicity, and correlates it again with the absence of fucose as claimed in the invention. Example 7 evaluates the correlation of fucose with antibody dependent cytotoxicity, demonstrating that the fucose lowers the antibody dependent cytotoxicity, while not affecting the binding of the antibody to its antigen, or changing the antibodies general characteristics. Example 8 evaluates another antibody with respect to the ratio of fucose present, and finds similar results. Example 9 determines the transcription product of the fucosyltransferase. Example 10 repeats example 9 with another cell line. Example 11 demonstrates that overexpression of such fucosyltransferase causes the otherwise-normal antibodies produced to have a lowered antibody-dependent cytotoxicity. Example 12 isolates the fucosyltransferase gene from CHO cells. Example 13 uses a gene-disruption technique to completely delete the activity of the fucosyltransferase in CHO cells, by removing at least exon 4 of α-1,6-fucosyltransferase and shows that antibodies produced form such cells has a higher level of antibody dependent cytotoxicity. Example 14 demonstrates the selection of lectin resistant cells, demonstrating that 2 of 3 cells produced have even higher antibody-dependent cytotoxicity. Examples 14 and 15 analyzes the lectin resistant cell lines, finding other enzymes in the pathways of glycosylation are altered. Example 16 demonstrates an exploration for other enzymes involved in glycosylation and how to isolate the genes encoding such enzymes. Example 17 demonstrates the isolation a GMD gene associated with glycosylation from CHO cells. Example 18 demonstrates the sugar chain analysis of conventionally-available antibodies.

While Applicant has shown that deletion of the activity of α-1,6-fucosyltransferase in CHO cells and expression of antibodies from such cells produces antibodies with higher antibody-dependent cytotoxicity, the Artisan would be able to reasonably predict, in view of the art and Applicants disclosure, that any mutation maintaining 80% homology to the structure of α-1,6-fucosyltransferase, or 80% sequence similarity, or comprising at least one mutation to such sequences would produce any functional, albeit less active α-1,6-fucosyltransferase than wild type, nor would the artisan be able to reasonably predict that a certain level of reduced activity would produce the required level of fucosylation in antibodies so produced which would raise the level of antibody dependent cytotoxicity.

The Quantity of Experimentation Needed to Make and/or Use the Invention

Because of the insufficiency of the working examples and direction and guidance provided by Applicant, the inherent unpredictability in the art, the state of the art, and the nature of the invention, even in the face of an advanced level of skill in the art, the Artisan would be required to perform a large amount of experimentation to make and/or use the invention within its fully-claimed scope. Moreover, outside the use of such CHO cells to produce antibodies with a higher level of antibody dependent cytotoxicity, the Artisan would find no use for any of these cells. Therefore, the Artisan would be required to experiment to find other uses, and to find the amounts and types of mutations in the enzyme that would produce the levels of glycosylations needed.

Conclusion

Because of the large amount of experimentation required to make and/or use the invention to its fully-claimed scope, such experimentation is considered undue, and therefore, the

claims are not enabled for their full scope. What is enabled are recombinant CHO comprising deletions in at least one α-1,6-fucosyltransferase gene, wherein the deletion of said gene encompasses at least exon 4, and further transformed with a gene encoding an antibody molecule, which antibody molecule so expressed in the CHO exhibits higher levels of antibody dependent cytotoxicity, but otherwise normal characteristics.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Lifely, et al. (1995) Glycobiology, 5(8): 813-22.

Lifely teaches a humanized IgG antibody which is expressed in, *inter alia*, CHO cells (ABSTRACT). As such, Lifely inherently teaches CHO cells into which a gene has been introduced encoding an antibody molecule. Moreover, as claimed by applicant, the characteristics of glycosylation required are inherently produced from such cells.

CONCLUSION

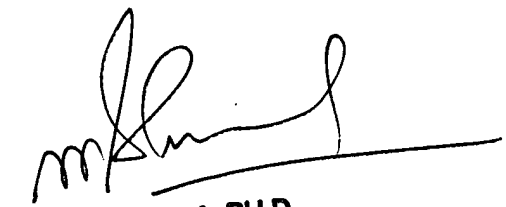
Claims 4, 12-19, 23, and 31-40 are free of the prior art of record.

No Claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M Kelly whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER